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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,100	07/22/2003	Santiago Munne		8781

7590 03/23/2007

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EXAMINER	
TON, THAIAN N	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,100	MUNNE, SANTIAGO	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment to the claims, filed 1/22/07, is found to be compliant and has been entered. Claims 1-4 are cancelled; claims 5-8 are newly added; claims 5-8 are pending and under current examination.

Applicants did not file a response directed to the rejections of record with the 1/22/07 submission, accordingly, the Examiner responds to the arguments set forth in Applicants' submission, mailed 8/4/06. This action is non-final.

Claim Objections

1. Claim 6 is objected to because of the following informalities:
   It appears that the claim has a typographical error, reciting a "stem line". It is suggested that the claim be rewritten to recite "stem cell line".
2. Claim 7 is objected to because of the following informalities:
   The term "mitomycin" is misspelled in part (b) of the claim. Appropriate correction is required.
3. Claim 8 is objected to because of the following informalities:
   The claim refers to "A" method of claim 7. There is only one method in claim 7, it is suggested the claim be amended to refer to "The" method of claim 7.

Oath/Declaration

Applicants' oath, filed 8/4/06, is proper and has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new ground of rejection.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments

Applicants' Arguments. Applicants' argue that their patent specification need only describe and show possession of the invention in its totality and that the Thomson patents and references teach how to make stem cells from "normal" non trisomically-derived disomic embryonic stem cells. Applicants argue that Thomson does not teach or disclose that trisomic cell lines can revert to "normal". Applicants present various pieces of case law, which are pertinent to written description (Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 USPQ 81 (Fed.Cir. 1986); reduction to practice and written description (Edwards, In re, 568 F.2d 1349, 196 USPQ 465 (CCPA 1978); and rejections under 102(b) 35 U.S.C.102(b)). C.f., In re Ruschig, 343 F.2d 965, 974, 145 USPQ 274, 282 (CCPA 1965) (Rejection of claimed compound in light of prior art genus based on Petering is not appropriate where the prior art does not disclose a small recognizable class of compounds with common properties). See page 4, 1st ¶ of the Response.

Response to Arguments. The Examiner notes that written description is a separate and distinct requirement from the enablement requirement. See MPEP §2163. In particular, to satisfy the written description requirement, the specification must describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the invention has *possession of the claimed invention.* The rejection of record is directed to enablement. In particular, Applicants arguments are not persuasive because none of the above-cited case law specifically addresses the instant enablement rejection. The Examiner directs Applicants to MPEP §2164, which states, "The enablement requirement refers to the requirement of 35 U.S.C. 112, first paragraph that the specification describe how to *make and how to use* the invention. The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent."

The Examiner provides specific reasoning in the body of this rejection (below) as to why the claimed invention is not enabling.

Applicants' Arguments. Applicants argue that they, "[C]an testify that I have assigned colleagues who are skilled in the art in making stem cells from these cell lines with only the specification and references detailed in this patent application and they have successfully isolated stem cells (RG44, RG56, RG92, RG93, RG94, RGK230) that have the characteristic epitopes of stem cells (SSEA-1, SSEA-3, SSEA-4, TRA 1-60, TRA 1-81, OCT 4, alkaline phosphatase)." See page 4, 2nd ¶ of the Response.

Response to Arguments. These arguments are not persuasive. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). In particular, Applicants' statement that many assigned colleagues skilled in the art have identified characteristics from stem cells that have the appropriate isotopes of stem cells (such as those also identified by Thomson, cited previously), does not provide an

appropriate affidavit or declaration supporting that any of the cell lines ((RG44, RG56, RG92, RG93, RG94, RGK230) are cell lines that are produced by the same methods as those disclosed in the as-filed specification, or that any of these cell lines are the ones that are disclosed in the as-filed specification. Thus, there is no nexus between the stem cell lines that Applicants recite, and the characteristics of the cell line(s) that are disclosed in the working example.

It is reiterated that the art teaches the specific, art-recognized characteristics of pluripotent cells (see Thomson, cited previously); however, specification is only directed to the karyotypic analysis of the embryonic cells (see Table 1). There is no guidance to show the isolation of inner cell mass cell from the embryos, and the subsequent analysis of the cells to show that they would indeed show the characteristics of embryonic stem cells.

Applicants' arguments with regard to the "inherent characteristic" of embryonic cells, with regard to claims 1-2 (see p. 4, 3rd ¶ of the Response), is not persuasive, because it is not directed to the rejected claims, which are claims 7-8 (previously claims 3-4). Claims 1-2 (now claims 5-6) are product claims, which are addressed under §102 rejection (see below); whereas claims 7-8 are directed to method claims, which are not found to be enabled for reasons of record. Applicants have not provided sufficient guidance or teachings with regard to the resultant cells that are produced by their method, such that one of skill in the art would recognize that they had the art-accepted characteristics of embryonic stem cells. Applicants have not shown that the cells are capable of differentiation into cells of the three germ layers, which indicates the differentiation potential of the cells.

Rejection

Nature of the Invention. The invention is directed to methods of producing disomic human embryonic cell lines by culturing trisomic human embryos onto mouse feeder cells, consisting of mouse embryonic fibroblast cells, wherein the

mouse embryonic fibroblast cells have been previously been mitotically inactivated by mitomycin C in gelatin-tissue culture dishes, maintain said mouse feeder cells using DMEM as claimed, supplementing the medium with human LIF, culturing the embryos in said medium until day 12, fixing and analyzing said embryonic cell lines, identifying and isolating disomic cell lines within said embryonic cell lines wherein disomic cell lines are produced.

Breadth of the claims. The breadth of the claims encompasses any embryonic cell line, including embryonic stem cells, and other cells which are embryonic, but not stem cells.

Guidance of the Specification/The Existence of Working Examples. The specification teaches chromosomally abnormal human embryos were cultured in sequential media, and the trophectoderm of the hatching blastocyst were biopsied to confirm chromosomal abnormality. The specification teaches that the remainder of the embryo was then plated on mouse embryonic fibroblast feeder layers. The embryos were then cultured until day 12, where the human cells were fixed and analyzed by FISH. A progressive increase from abnormal to normal cells was found between day 6 and day 12, and that by day 12, all 7 cultured embryos were mosaics. The specification teaches that this observed reduction in trisomic cells cannot be due to the non-survival of trisomic embryos in culture, and that the most reasonable explanation is that the trisomic cells revert to disomic cells in extended culture. See pages 3-4 of the specification and Table 1 (page 6). The specification teaches that this method can be used to obtain chromosomally normal stem cells from trisomic embryos. The specification provides a prophetic example of how to derive a disomic cell line from these cells (see pp. 6-7, Method for derivation of single-cell clones).

State of the Art/Predictability of the Art. The breadth of the claims encompasses any type of embryonic cells, which encompass embryonic stem cells, which are art-recognized as pluripotent and exhibit characteristics of embryonic stem cells. For example, Thomson *et al.* (**PNAS**, 92:7844-7848 (August 1995)) teach

the specific, art-recognized characteristics of pluripotent cells - that these cells remain undifferentiated in culture in continuous passage, maintain a normal karyotype, express appropriate cell markers [alkaline phosphatase, SSEA-3, SSEA-4, TRA-160-, TRA-1-81] and, when injected into SCID mice, they consistently differentiate into derivatives of all three germ layers. See *Abstract* and p. 7845-7846. Although the specification provides guidance to show that embryonic cells can be produced using the claimed methods, there is no guidance with regard to the particular markers expressed by these cells, or that these cells have differentiation potential of pluripotent cells. The specification is only directed to the karyotypic analysis of the embryonic cells (see Table 1). There is no guidance to show the isolation of inner cell mass cell from the embryos, and the subsequent analysis of the cells to show that they would indeed show the characteristics of embryonic stem cells. Indeed, the specification states that in the initial study, trophectoderm and inner cell mass cells were not independently fixed for further FISH analysis (see paragraph 13, page 4). Furthermore, the specification clearly states that the yield of disomic cells from the chromosomally abnormal embryos is extremely low, as only 7/44 embryos developed in culture until day 12. See p. 5, paragraph 18.

The Amount of Experimentation Necessary. The claims are not enabling for the following reasons:

1. The working examples do not provide sufficient guidance or teachings with regard to the characterization of the embryonic cells that are produced by the claimed method. In particular, the specification provides no guidance, other than the karyotypic analysis of the resultant disomic cells. There is no guidance with regard to if the cells are pluripotent, express appropriate markers, or have any of the art-recognized characteristics of embryonic stem cells. As stated in the prior Office action,

2. The specification only provides a contemplated use with regard to embryonic stem cells. See, for example, page 3, paragraph 8 of the specification,

which discusses the isolation of stem cells from the resultant diploid cells. There is no teachings or guidance provided by the specification with regard to the isolation of non-embryonic stem cells (i.*e.*, "embryonic cells") from the diploid cell lines produced, or what these embryonic cells (which are not stem cells) would be used for.

The standard, under 112, 1st ¶, for enablement is that the specification must provide guidance on how to make and use the claimed invention. One of skill would not be able to make embryonic *stem* cells from the teachings of the specification, because there is no guidance with regard to the disomic cell lines that are produced from the trisomic embryos, in particular, that they have any of the art-recognized characteristics of embryonic stem cells. One of skill would not know how to make and use embryonic cells that are not stem cells, because the specification provides no guidance with regard to the isolation or characterization of these cells, or what the cells would be used for.

Accordingly, in view of the state of the art of embryonic stem cells, namely the specific, art-recognized characteristics of such cells, the lack of teaching, guidance or characterization of cells produced by the claimed method, other than karytotypic analysis of the cells, the unpredictable state of the art of producing embryonic stem cells, and the lack of guidance or teaching provided by the specification to overcome these unpredictibilities, the lack of teaching or guidance with regard to how to make embryonic cells that are not stem cells, it would have required undue experimentation for one of skill in the art to make and use the claimed disomic cell lines.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "said disomic cell lines". There is insufficient antecedent basis for this limitation in the claim. Claim 5 only refers to a single disomic cell line, not multiple cell lines. Appropriate correction is required.

Claim 7 is indefinite for the following reasons:

1. Part (c) of the claim refers to "said medium". It is unclear which medium this refers to, because step (b) refers to using "DMEM without sodium pyruvate, glucose 4500 mgL-1 supplemented with 20% fetal bovine serum, 0.1 mM -mercaptoethanol, 1% non-essential amino acids, 1 mM L-glutamine, 50 units ml L-1 penicillin." Therefore the only "medium" in part (b) is the DMEM. If Applicants intend to include the other components recited in part (b), it is suggested that Applicants' amended the claim to recite, for example, "medium comprising...".

2. The claim recites the limitation "said embryonic cell lines" in part (e) of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 8 depends from claim 7.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicants do not provide any specifically argument with regard to each of the rejections; therefore, the Examiner addresses Applicants' arguments as they generally apply to the rejections of record.

Applicants' Arguments. Applicants argue that the product claims (claims 1-2, now represented by newly added claims 5-6) are not anticipated by the art of record (Thomson (1996); Shamblott (1998); Thomson (1995); Thomson (2001)).

Applicants provide several pieces of case law that are not pertinent to the claimed rejection, because they are directed to written description, a rejection under 112, 1st paragraph. The instant rejection is under 102(b). In particular, it appears that Applicants are arguing that the stem cell lines taught by the art are made by an entirely different process than that which is instantly claimed (see page 5, 4th ¶ of the Response). Applicants have argued that their, "trisomically derived disomic cell lines have structural and karyotypic characteristics different from Thomson's non-trisomically derived disomic cell lines. It is statistically unlikely that such a complex structure as a cell isolated for different selected criteria would converge into identical cell types." See p. 5, 5th ¶ of the Response.

Applicants argue that none of the Thomson references, nor the Shamblott anticipate trisomically derived disomic cell lines and stem cells therein, because there is no mention of trisomy in any of the references presented by the Examiner, and anticipation requires all the elements of the claim *a priori* and not just a mix of elements and hindsight combination *a posteriori.* See page 5, last ¶ of the Response.

Response to Arguments. These arguments have been fully considered, but are not persuasive. The Examiner directs Applicants to MPEP §2113, which details Product-By-Process claims. It is reiterated that the instant claims are product-by-process claims, and that, "The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product."

The instant claims are directed to a disomic cell line derived from trisomic embryos (claim 5), and a stem cell line derived from the disomic cell line of claim 5 (claim 6). The specification teaches that extended culture of trisomic human embryos results in "diploid cells that are undifferentiated and contain stem cells" (see page 3, paragraph 8 of the specification). Furthermore, the working examples of the specification teach the production of chromosomally/karyotypically normal embryo cells that are derived from abnormal embryos (see p. 5, paragraph 16 of the specification). Accordingly, the Examiner interprets the claimed invention as follows: claim 5 only requires that the cell lines be disomic; and claim 6 requires that the disomic cell line be a stem cell line. Therefore, art that shows that a particular cell line is disomic (*i.e.*, diploid) and is a stem cell line (for example, an embryonic stem cell line), anticipates the claims.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, under 35 U.S.C. 102 (b) as being anticipated by Thomson [WO 96/22362, published 25 July 1996]. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 11/23/05.

Thomson teach the isolation and purification of primate embryonic stem cells that are capable of indefinite proliferation *in vitro* in an undifferentiated state, are capable of differentiation to derivatives of all three embryonic germ layers, and maintain a normal karyotype throughout prolonged culture. The pluripotent cells are negative for SSEA-1, positive for the SSEA-3 marker, positive for the SSEA-4 marker, TRA-1-60, TRA-1-81 and alkaline phosphatase. Thomson teach that the primate cells can continue to proliferate in an undifferentiated state for at least one year. See p. 7, lines 9-32. Thomson teach that tumors formed after injection of rhesus ES cells into the hindleg muscles of SCID mice [see Figure 5].

Accordingly, Thomson *et al.* anticipate the claimed invention because they teach a disomic cell line, and particularly, a disomic, embryonic stem cell line.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, as being anticipated by Shamblott *et al.* [PNAS, 95:13726-13731 (1998)].

Shamblott teach that human pluripotent stem cells were isolated from gonadal ridges and mesenteries of 5- to 9-week postfertilization human embryos. Cells were cultured and subsequently passaged onto a mouse STO fibroblast feeder layer. Shamblott teach that embryoid bodies were collected from cultures and immediately embedded or replated into single wells [under conditions using mouse embryo fibroblasts, human fetal fibroblasts, or gelatin-coated tissue culture, see p. 13729, 1st column, 1st full ¶] and cultured for 14 days in the absence of hrLIF, hrbFGF and forskolin. See pp. 13726-13727, *Materials and Methods*. They teach that immunohistochemical analysis of embryoid bodies demonstrated that the cells could differentiate into a variety of cell types, including derivatives of the three embryonic germ layers. See p. 13729, 2nd column, 1st full ¶. They teach that these cellsl are karyotypically normal (see Abstract, and Material and Methods).

As Shamblott *et al.* teach a disomic cell line, and in particular, an disomic, embryonic stem cell line, they anticipate the claimed invention.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, as being anticipated by Thomson *et al.* (PNAS, 92:7844-7848 (August 1995)).

Thomson *et al.* teach pluripotent primate embryonic stem cells, isolated from a rhesus monkey blastocyst. They teach that these cells remain undifferentiated in culture in continuous passage, maintain a normal karyotype, express appropriate cell markers [alkaline phosphatase, SSEA-3, SSEA-4, TRA-160-, TRA-1-81] and, when injected into SCID mice, they consistently differentiate into derivatives of all three germ layers. See *Abstract* and p. 7845-7846.

Accordingly, as Thomson teach a disomic stem cell line, they anticipate the claimed invention.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, as being anticipated by Thomson [U.S. Pat. No. 6,200,806 B1, March 13, 2001].

Thomson teach the preparation of a primate embryonic stem cell line that has expresses the cell surface markers characteristic of embryonic stem cells, have normal karyotypes, are able to proliferate in an undifferentiated state in continuous culture, and the ability to differentiate into all tissues derived from all three embryonic germ layers (see Abstract and claims).

Thus, because Thomson teach a karyotypically normal, disomic human embryonic stem cell line, they anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Thaian Ton

THAIAN N. TON
PATENT EXAMINER